IV THE PARADOXICAL TREND OF LUNG CANCER MORTALITY

The tremendous rise in lung cancer deaths has been accepted by the Surgeon General's Advisory Committee as unequivocal evidence of a true increase in the disease but there are many aspects of the problem that challenge this conclusion. An objective evaluation requires consideration of (1) the difficulties involved in the compilation of comparative statistical data and (2) the trend of lung cancer mortality during the past 35 years.

The collection of annual vital statistics based on information recorded on death certificates was begun in 1900. The original registration area included 10 states, a number of cities in non-registered states, and represented a total population of 30,765,618 (202). Expansion of the registration area was not uniform because of the withdrawal and readmission of previously registered states. In 1905, the registration area included 40 per cent of the population of the United States; in 1915, the area included 68 per cent and in 1925, the area included 90 per cent. Annual mortality data for the whole country have been in existence only since 1933.

Variations in Geographic Distribution

Mortality rates for lung cancer varied among the states and were often directly proportional to the number of years that the states had been included in the Death Registration

area. As late as 1949, there were 8 states with significantly higher standardized rates and 19 states with significantly lower standardized rates in comparison with the total United States experience (203) (204). The states that had been registered in 1914 had a much higher rate in 1949 than the non-registered states. It is evident, therefore, that comparable mortality data for the entire United States prior to 1933 are not available. The admission of new states into the registration area had the effect of artificially lowering the lung cancer mortality in the earlier decades.

Geographic variations in lung cancer death rates continued for many years suggesting the implication of factors such as diagnostic sophistication, case finding surveys, and accuracy in certification. Between 1940 and 1950 there existed a wide disparity in age specific death rates among the various regions of the United States with the highest rates recorded in the Middle Atlantic and New England areas and the lowest rates in most of the Central and Northwest areas (205). The lung cancer death rates in 1950 in North Dakota, Arkansas, Idaho, New Mexico, North Carolina, and Utah were approximately one half of those recorded for New York, New Jersey, Maryland, and Delaware. Geographic location was not the only major difference between the areas with high rates and those with low rates. In general, the states with the highest recorded mortality from lung cancer were more industrialized, more urbanized, and had a far greater number of physicians per 100,000 of population than the states

with the low rates which were predominantly in agricultural or mountain regions.

There were certain characteristics of the increase in lung cancer between 1940 and 1950 that have an important bearing on the entire problem. The increase in lung cancer mortality was most evident in the states which had the lowest rates in 1940 and the smallest number of physicians. In South Carolina, with 74 physicians per 100,000 of population, the lung cancer death rate rose from 1.9 per 100,000 in 1940 to 8.5 per 100,000 in 1950, an increase of 347 per cent. A similar experience was noted in Arkansas with 94 physicians per 100,000 of population. The lung cancer death rate rose from 2.2 per 100,000 in 1940 to 8.3 per 100,000 in 1950, an increase of 277 per cent. Among states with large numbers of physicians and with relatively high lung cancer death rates in 1940, the increase was far less dramatic. In Massachusetts, with 183 physicians per 100,000 of population, the death rate rose from 10.5 per 100,000 in 1940 to 16.4 per 100,000 in 1950, an increase of 56 per cent. A similar experience was noted in New York with 203 physicians per 100,000 of population where the death rate rose from 13.5 per 100,000 in 1940 to 20.9 per 100,000 in 1950, an increase of 55 per cent.

The above data show some very significant correlations. All the states showed a rise in lung cancer mortality between 1940 and 1950 but the greatest increases occurred in the states with the lowest rates and the smallest physician to

population ratios in 1940. It is very apparent, therefore, that the differences in the magnitude of the increase among the various states was not dependent, per se, on geographic distribution but on the medical facilities available for the detection of the disease. During the decade, 1940-1950, the techniques for diagnosing lung cancer became more and more available to all segments of the country and the disparity in lung cancer mortality among the states began to diminish.

Faulty Certification

Although autopsy studies are not necessarily representative of the population they represent, it is interesting to note that a study by Farber (174) in 1954 revealed that less than 40 per cent of 1,070 cases of lung cancer had been diagnosed prior to autopsy. It is impossible to estimate how many lung cancer cases were undetected in the earlier decades of this century. However, if only a small percentage of the cases certified as dying of tuberculosis or pneumonia had been erroneously diagnosed, the lung cancer mortality rate would have been comparable to current trends.

For many years, tuberculosis and pneumonia comprised the major causes of death attributed to respiratory diseases. In 1900, the crude death rates for respiratory tuberculosis and for pneumonia were, respectively, 180.5 per 100,000. The death rate for bronchitis was 45.7 per 100,000 and for influenza it was 22.9 per 100,000. The other respiratory diseases, combined, had a death rate of 26.7 per 100,000. There were no death rates recorded for lung cancer until 1914. During successive years, the death rates for all respiratory diseases declined and in 1914 the crude death rate for respiratory

tuberculosis was 123.1 per 100,000 and for pneumonia, it was 127.0 per 100,000. The death rates for influenza, bronchitis, and other respiratory diseases also showed striking reductions.

The overall crude death rate of lung cancer in 1914 was 0.6 per 100,000 and in 1950, it was 12.5 per 100,000. According to the calculations of Gilliam (206), the following percentages of diagnostic error in deaths attributed to tuberculosis and other respiratory diseases would be necessary for the 1914 lung cancer mortality to equal that of 1950. Among the deaths attributed to tuberculosis, faulty certification in 11.2 per cent of the males and 2.8 per cent of the females would have resulted in equalization of lung cancer mortality between 1914 and 1950. When pneumonia and the various other respiratory diseases are considered as a group, an error of 5.0 per cent among the males and 1.1 per cent among the females would also have resulted in parity.

The consequences of faulty certification may also be contemplated by postulating the effect of a specific percentage of diagnostic error. In 1914, the age-adjusted death rate of lung cancer in white males over 35 years of age was 0.8 per 100,000. If 10 per cent of the deaths attributed to pulmonary tuberculosis had actually been caused by lung cancer, the death rate would have been 9.5 per 100,000. The increase in lung cancer mortality would then have been 2-fold instead of 26-fold. If the diagnostic error had been as little as 5 per cent, the increase between 1914 and 1950 would have been only 4-fold.

The same postulation applied to white females would have resulted in no increase in lung cancer mortality between 1914 and 1950 if the diagnostic error had been 10 per cent and less than 2-fold if the error had been 5 per cent.

The effect of faulty certification of all respiratory diseases, combined, may be summarized as follows. If 5 per cent of the cases so certified had actually died of lung cancer, the increase in lung cancer mortality among males over 35 years of age would only have been 2-fold between 1914 and 1950; among females, the mortality trend would have been reversed with more females dying of lung cancer in 1914 than in 1950. At the 3 per cent level of error, the increase among males would have been 3-fold and, among females, there would have been no increase.

Experienced physicians will find little difficulty in postulating an error of the magnitude of 10 per cent in the clinical diagnosis of respiratory diseases, particularly, in an era devoid of x-ray examination, bronchoscopy, and thoracotomy. Large scale autopsy studies (174) previously referred to showed an error of more than 60 per cent in the diagnosis of lung cancer when all the modern facilities for the detection of the disease were readily available.

The Effect of Revisions of Classification

Until relatively recently, the various rubrics assigned to lung cancer in the Manual of International List of

of Causes of Death made comparisons of mortality rates exceedingly difficult if not impossible. Authoritative statements that the death rate from lung cancer increased in white males from 3.9 per cent in 1930 to 35.4 per cent in 1960 and in non-white males from 1.6 per cent in 1930 to 33.8 per cent in 1960 call for circumspect interpretation. A true evaluation of the mortality data prior to 1950 requires consideration of not only the limited facilities available for diagnosis but also the difficulties of statistical comparability because of the decennial revisions of the code of classification.

Between 1914 and 1920, the classification of deaths ascribed to cancer of the respiratory system was based on the 1909 revision of the International List of Causes of Death, supplemented by subtitles added by the United States Bureau of Census. In this classification lung cancer was listed under the ambiguous title, "Cancer and other malignant tumors of other organs or of organs not specified" and was placed in category 45B which also included cancer of the anterior mediastinum, lung, mediastinal gland, mediastinum, pleura, bronchi, lung and pleura. In classification 45X, cancer of the bronchi was placed in the same group with cancer of the accessory sinus, antrum, posterior nares, and trachea. The code was revised in 1920 and a different calssification was used between 1921 and 1929 with titles 49B and 49X corresponding to titles 45B and 45X of the 1909 revision. The list was revised again in 1929 and the new titles were used between 1930 and 1938. In this revision

cancer of the respiratory system became a specific category for the first time and lung cancer was listed under items 47B and 47C. The title of 47B referred to cancer of the lungs and pleura and included subtitles of cancer of the anterior mediastinum, lung, mediastinal gland, mediastinum, and pleura. The title 47C referred to cancer of other respiratory organs and included cancer of the bronchi, nasal cavity, nasopharynx, nostril, posterior nares, and trachea.

The fifth revision of the international code occurred in 1938 and was used between 1939 and 1948. Title 47 referred to cancer of the respiratory system and for the first time included a subtitle 47 (c) with separate designations for bronchogenic carcinoma and cancer of the bronchus. There was also a subtitle 47 (d) for cancer of the lung and pulmonary cancer; a subtitle 47 (e) for cancer of the pleura; and a subtitle 47 (f) for cancer of the mediastinum and unspecified sites. To further add to the confusion, there was also a title 55 (e) for cancer of other and unspecified organs that included designations for cancer of the chest, thoracic cavity and thorax. It is very apparent from the profusion of terminology that the authors of the international code of classification had very little knowledge of the pathogenesis of lung cancer nor were they even aware that bronchogenic carcinoma and lung cancer were the same disease. The greatest indictment against the classification is that for decades it did not even recognize bronchogenic carcinoma as a specific entity thereby discouraging its certification as

a primary cause of death. The term, bronchogenic carcinoma, was introduced for the first time in 1939 and, in the succeeding decade, the crude death rate increased more than 3-fold.

The sixth revision of the International List of Causes of Death was made in 1948 and has been in use since 1949. This revision was a major step toward clarification of lung cancer mortality but failed to differentiate entirely between primary and secondary lung cancer. Title 162 refers to primary cancer of the bronchus, lung, pleura and trachea. Title 163 refers to the same categories unspecified as to primary or secondary origin. Title 164 refers to cancer of the mediastinum and thoracic organs and title 165 refers to secondary cancer of the bronchus, lung, mediastinum, pleura, thorax, trachea, and respiratory organs not otherwise specified.

A seventh revision of the international classification is expected to be implemented in 1968. In this nomenclature, title 162.1 will include only primary cancer of the bronchus and lung and title 197 will include secondary lung cancer. Whether this classification will contribute to further confusion of mortality data or further clarification will depend on the interest of clinicians and pathologists in differentiating between primary and secondary lung cancer. In the previcus classification the category, 163, included lung cancer unspecified as to whether primary or secondary. In the contemplated revision, if the death certificate fails to specify secondary lung cancer, the case will be automatically listed as

primary lung cancer thereby artificially increasing the incidence of primary lung cancer. Inasmuch as the differentiation between primary and metastatic lung cancer may not be possible without autopsy, the new classification may create as many problems in statistical accuracy as it solves.

Another factor which contributed to the obscurity of lung cancer mortality data was the set of regulations governing multiple causes of death (207) (208). Prior to 1949, when death certificates listed two or more sites of cancer, the presumptive primary site was arbitrarily coded in the vital statistics. The 1925 edition of the Manual of Joint Causes of Death specified that when lung cancer coexisted with cancer of the digestive tract, buccal cavity, female genital organs, breast, or skin, the latter sites were to be given precedence and tabulated as the primary lesion. The 1933 and 1939 editions of the manual contained a slight revision in favor of lung cancer —— cancer of the skin when reported jointly with lung cancer was no longer classified as the primary disease. Mortality data on lung cancer was therefore influenced for more than 3 decades by predetermined rules of tabulation having no bearing, whatsoever, on the true prevalence of the disease.

The Decline in the Rate of Increase

In discussing lung cancer mortality trends it should be emphasized that the term, lung cancer, is used merely for expediency and that what is actually under comparison is a

group of rubrics under the general heading of "cancer of the respiratory system other than larynx". Deaths attributed to bronchogenic carcinoma prior to 1930 are unidentifiable. There are many limitations of the available statistical data (209) but the overall trend of lung cancer mortality follows a pattern that is clinically significant. The increase in lung cancer deaths has been viewed with alarm with dire extrapolative forebodings of skyrocketing future death rates. In actuality, the trend of lung cancer mortality has been far more characteristic of diagnostic acumen than of epidemic spread. For more than three decades there has been a progressive decline in the rate of increase tending toward the same stabilization that occurred in other cancers in which diagnostic techniques have remained unchanged for many years.

Statistical studies by Dorn (210), Gover (211), Gilliam, et al. (212), Gordon, et al.(213) and Milmore (204) show that the greatest increase in lung cancer mortality occurred during the early decades of this century and that the rise began simultaneously for all age groups. In 1914, when the registration area comprised 67 per cent of the total population of the United States, there were 371 lung cancer deaths reported with an adjusted standardized death rate of 0.66 per 100,000. Between 1914 and 1930-1932, the age adjusted mortality rate for white males increased 393 per cent, or about 23 per cent annually. The corresponding increase for white females was 228 per cent, or about 13 per cent annually. Since then, there has been a progressive increase in the total number of lung cancer deaths but

there has been a consistent decline in the rate at which this has occurred.

In the period, 1930-1932, the adjusted death rate among white males was 4.23 per 100,000; in the period 1939-1941, the death rate was 10.00 per 100,000 in the period 1951-1953, the death rate was 24.43 per 100,000 and in the period 1957-1958, the rate was 33.22 per 100,000. Concomitant with the steady rise in death rate, there also occurred a gradual lowering of the rate of increase during successive periods. Between 1930 and 1935, the annual increase was 10.2 per cent; between 1939 and 1944, the annual increase was 7.0 per cent; between 1954 and 1958, the annual increase was 5.0 per cent, less than half prevailing three decades previously. A similar phenomenon was observed among white females. The adjusted death rate rose from 2.34 per 100,000 in the period 1930-1932 to 5.24 per 100,000 in the period 1957-1958 but the rate of increase declined from 5.6 per cent annually between 1930 and 1935 to 2.0 per cent annually between 1954 and 1958.

Correlation of death rates with age distribution reveals that the major component of the increase in lung cancer was contributed by persons in the 6th decade and older. The rate of increase is declining for all age groups but is more marked in the younger than in the older age groups. This trend is compatible with greater clinical experience in diagnosing lung cancer since the disease occurs predominantly in the older age groups. Among females the declining rate of increase is even more

striking than that shown by the males and has been fairly constant for all age groups. This, too, is a reflection of increased clinical experience which has shown that lung cancer is chiefly a disease of males. Studies of the non-white population are limited but the available data are informative. The lung cancer mortality rates recorded for the non-white population in 1930 were far lower than those of the white population but increased rapidly thereafter almost achieving equality by 1958. This is consistent with the marked improvement in medical facilities available to the non-white population in recent years. Since 1950, the rate of increase has also been declining for the non-white population.

The declining rate of increase in clinically diagnosed lung cancer followed a pattern similar to that observed when the diagnosis was established only at autopsy. Corresponding to the period of expanding knowledge of the pathology of the disease, there was a marked rise in autopsy incidence followed by a decline in the rate of increase. At the Moabit Hospital in Berlin, Wahl (214) found a 300 per cent increase in the ratio of lung cancer to all cancers between 1917 and 1923; the following year the rate of increase had declined to 17 per cent. Schonherr (215) reported similar findings at the Pathologic Hygienic Institute of Chemmitz. Between the periods 1898-1916 and 1919-1922 there was a 110 per cent increase followed by a decline to 24 per cent in the next four years. Materna (216), at the Troppau Pathologic Institute found the increase of lung cancer among all

cancers to be 240 per cent between the periods 1912-1914 and 1915-1917; between the latter period and 1921-1923, the increase was only 12 per cent. Schlesinger (217) reported an increase of 120 per cent at the Leipzig Pathologic Institute between the periods 1900-1906 and 1914-1918; between 1914-1918 and 1924-1929, the increase was 18 per cent. At the Prague Pathologic Institute, Holzer (218) found the increase of lung cancer among all cancers to be 190 per cent between the periods 1895-1899 and 1905-1909; 110 per cent between 1905-1909 and 1915-1919; and 66 per cent between 1915-1919 and 1920-1924. Maxwell and Nicholson (219) found an increase of 100 per cent at the St. Bartholomew's Hospital between the periods 1884-1888 and 1894-1898 and no increase between the latter period and 1904-1908.

Claude Bernard's dictum of looking beyond the statistical data is most applicable in evaluating lung cancer mortality. The progressive decline in the rate of increase suggests that the image of a lung cancer epidemic is an illusion created by the magic of numbers. The rise from 2,357 lung cancer deaths in 1930 to 45,838 in 1964 seems, at first glance, to be irrefutable proof of an absolute increase. However, if the rise is studied by lustrums there emerges a pattern completely compatible with the concept that the increase was not real but the effect of improved diagnostic facilities. Between 1930 and 1935, lung cancer deaths increased 79 per cent; between 1935 and 1940, the increase was 68 per cent; between 1940 and 1945, the increase was 53 per cent; between 1945 and 1950, the increase rose to

67 per cent but fell again between 1950 and 1955 to 46 per cent; between 1955 and 1960, the increase was 36 per cent; and between 1960 and 1965, the increase was only 34 per cent.

Confirmation of the peculiar trend in lung cancer mortality is available from sources other than the official national statistics. A study of Metropolitan Life Insurance Company policyholders by Dublin and Lotka (220) showed that for white males over 45 years of age, the age standardized death rate from lung cancer rose from 3.4 per 100,000 in 1917 to 21.2 per 100,000 in 1935. For all white males (1-74 years) the increase was from 0.9 per 100,000 in 1917 to 4.7 per 100,000 in 1935. The data for males over 45 years are more significant inasmuch as lung cancer occurs predominantly in older age groups but both categories showed annual increases of approximately 10 per cent. For white females, over 45 years of age, the age standardized death rate rose from 2.7 per 100,000 in 1917 to 7.6 per 100,000 in 1935 and, for all females, from 0.7 to 1.9 per 100,000. The annual rate of increase for both categories was approximately 5.5 per cent. The statistical data from this particular segment of the population paralleled the national census figures, again emphasizing that the highest rates of increase in lung cancer mortality occurred paradoxically during the period of growing awareness of the disease rather during the later era of sophisticated diagnostic facilities.

There are no lung cancer mortality statistics available for New York State prior to 1931 when 615 cases were

reported. In 1935, there were 1,006 lung cancer deaths representing an increase of 64 per cent. In 1940, there were 1,440 deaths with an increase of 43 per cent in the previous lustrum. Between 1945 and 1950, the increase in lung cancer deaths was 33 per cent. In 1965, there were 5,429 lung cancer deaths but the increase between 1960 and 1965 was down to 22 per cent. The trend of lung cancer mortality in New York State is similar to that of the nation and, because of the greater availability of diagnostic facilities, characterizes the decline in the rate of increase even more vividly.

The leveling off of the increase in lung cancer mortality is not a unique experience limited to the United States but has also been noted by Clemmesen (221) in Denmark and Springett (222) in England and Wales. In the latter study, there were three times an many lung cancer deaths in 1963 as in 1946 but the increase was confined to the older age groups. Under 45 years of age there was no increase in lung cancer deaths; in the age group 45-54 years, the number of deaths increased but the proportion for the age group decreased; in the age group 55-64 years, the number of deaths remained unchanged. There was an increase in the number of deaths for ages over 64 years with the proportion rising from 24 to 34 per cent; over 75 years of age, the increase was from 6 to 13 per cent.

It is impossible to reconcile a declining rate of increase in lung cancer mortality with the epidemic concept. The deceleration of the rate of increase implies that there has been

a relatively fixed prevalence of the disease in the population and that expansion of interest and diagnostic facilities has resulted in the recognition of a greater number of cases each year leaving proportionately fewer cases undiagnosed. The trend toward progressive decline of the rate of increase is crystal clear and, if unabated, will ultimately produce a standardization of the age adjusted mortality rate of lung cancer even though the total number of cases may continue to rise because of the increasing longevity (223) of the population. It must also be emphasized that while improved diagnostic techniques yield more cases of lung cancer, they also tend to eliminate the erroneously diagnosed cases of pulmonary metastases that simulate bronchogenic carcinoma.

The epidemic concept of the rise in lung cancer mortality has carried with it the implication that the increase was the direct result of the increased consumption of cigarettes. Observations of Gilliam (224) made more than a decade ago are still very applicable to the subject, "It is clear that this hypothesis in its entirety is untenable if the recorded increase is an artifact due to appreciable changes in diagnostic accuracy".

V THE BIOLOGIC FEATURES OF LUNG CANCER

The predilection of lung cancer for males was attributed by the Surgeon General's Advisory Committee to heavier smoking habits and presented as evidence incriminating cigarettes. The absurdity of this assertion becomes readily apparent when it is realized that lung cancer was predominantly a disease of males

when cigarette smoking was a rarity. Furthermore, the prodigious smoking of females during the past 4 decades has had no effect on decreasing the disparity of sex distribution.

Male Predominance

The affinity of lung cancer for males is a biologic characteristic of the disease. Sex predilection occurs commonly in a variety of diseases and an excellent illustration is cancer of the breast which occurs preponderantly in females. There were a great many studies of lung cancer during an era in which cigarette smoking was virtually non-existent and all showed a remarkable consistency in sex distribution. Hare (95), in a study of lung cancer covering the period 1830 to 1880, found 90 cases in males and 33 cases in females. Adler's (116) collected series of cases spanned the years 1842 to 1911 and included 269 males and 93 females. In a report of the experiences of the teaching hospitals in Great Britain between 1894 and 1918, Passey (225) found 579 cases of lung cancer in males and 182 cases in females. In 1892, Harris (30) reported on a combined study of St. Bartholomew's Hospital and the City of London Hospital for Diseases of the Chest and found that lung cancer occurred three times as often in males as in females. Similar ratios of 3:1 favoring the male were reported from Germany by Passler (77), Riechelman (226), Briese (112), and Karrenstein (115) during the late 19th and early 20th centuries. In the United States, King (83) found a 4:1 ratio in Boston covering the period, 1875-1914. Weller (227) who

was among the first American pathologists to become interested in lung cancer also found a 4:1 ratio in a collected series of cases between 1878 and 1912.

Despite the variety of the sources of the material studied, there was unanimous agreement on male predilection of the disease before the era of cigarette smoking. It is also of significance that many of the autopsy reports in the 19th century and early 20th century revealed sex ratios as high or higher than those found in recent studies. Wolf (105), reported a 6:1 ratio from the Dresden municipal hospitals for the period, 1885-1884. Eichengrun (114) found a 6.4:1 ratio in Cologne between 1902 and 1919. Rau (228) found a 6.5:1 ratio in Dresden-Friedrichstadt between 1909 and 1914. Feilchenfeld (100) reported a 10:1 ratio in Berlin between 1894 and 1900 and in Leipzig, Lenhartz (82). found a 13:1 ratio.

Inasmuch as lung cancer is predominantly a disease of males, improvements in diagnostic accuracy resulted in proportionately more cases detected in males and a progressive rise in the sex ratio. This phenomenon was already apparent in the early decades of the 20th century when most cases were diagnosed by autopsy and became even more obvious when the disease began to be diagnosed clinically. At the Moabit and Urban Hospitals in Berlin, Peters (111) noted a 3:1 ratio between 1905 and 1908 and a 5:1 ratio in the same institutions between 1917 and 1922. Since 1930, lung cancer certification without autopsy has increased manifold. The early reports showed the distribution of the disease

to be almost equal between the sexes but, as clinical diagnostic accuracy improved, male predominance became very evident paralleling the autopsy reports of the 19th and early 20th centuries. An excellent illustration of the relationship between diagnostic accuracy and the sex ratio was provided by Clemmensen and Busk (229) who observed that in Denmark, between 1936 and 1945, the overall ratio was 2.4:1 whereas in a special chest clinic in Copenhagen, the ratio was 7.2:1.

The effect of diagnostic accuracy on the sex distribution of lung cancer is also emphasized in the observations of Ibrahim (230) who found, in 1954, a sex ratio of 9:1 in non-cigarette smokers at the Dacca Medical College in East Pakistan where pulmonary diagnostic facilities had been recently established. Among the lowest sex ratios found within the past decade was a report by Farago (231), from Papau and New Guinea covering the period 1958-1962. In those regions of the world, cigarette smoking is widespread but facilities for the diagnosis of lung cancer are still very limited resulting in a sex ratio of only 4:1.

During the past 35 years there has been a progressive rise in the sex ratio in the United States lung cancer mortality statistics. In 1930, there were 1,818 lung cancer deaths reported in males and 1,019 in females giving a ratio of 1.8:1. During the succeeding decade there was an upsurge of interest in the disease and facilities for diagnosis became more available. This was reflected in both an increase in lung cancer mortality and in the sex ratio. In 1940, there were 6,057 male

deaths and 2,029 female deaths giving a ratio of 3:1. Between 1940 and 1950, advances in diagnosis were even more striking, particularly, the use of exploratory thoracic surgery as a diagnostic tool and the increasing utilization of the Papanicolaou technique for sputum and bronchial aspirate examination. In 1950, there were 14,922 male lung cancer deaths and 3,391 female lung cancer deaths, giving a sex ratio of 4.4:1. During the next decade it was very evident that the increase in lung cancer mortality was chiefly confined to males. In 1960, there were 30,800 male deaths and 5,000 female deaths giving a sex ratio of 6.2:1.

Lung Cancer in Females

The prodigious increase in cigarette consumption by females for more than 4 decades has not been reflected in a corresponding increase of lung cancer. A survey (232) of smoking patterns in 1955 by the United States Bureau of the Census revealed that approximately 46,000,000 persons had been regular cigarette smokers and, of these, 15,000,000 were females over 18 years of age. The survey acknowledged that it had underestimated cigarette consumption by 15 per cent on the basis of tax data and common observation suggests even a greater margin of error. Current estimates point to more than 70,000,000 cigarette smokers with a proportionate increase among females. If cigarette smoking is a potent carcinogenic agent it should have affected lung cancer mortality by this time resulting in an equalization of

the sex ratio which in 1964 was 6.4:1. Diagnostic facilities have been equally available to both sexes for many years.

The lung cancer death rate in females increased from 1.5 per 100,000 in 1930 to 7.1 per 100,000 in 1964 but still remains far below the rate of 41.4 per 100,000 for males (233). It is inconceivable for such a difference in lung cancer mortality to exist if cigarette smoking was a significant causal factor in lung cancer. The proponents of the smoking-cancer hypothesis reconcile the disparity with claims that females have begun to smoke relatively recently and that eventually the lung cancer rates will equal those of males. The truth is that females have been smoking for more than 40 years and that sufficient time has elapsed for the alleged carcinogenic action of tobacco to express itself, if indeed, it exists at all. Between 1959 and 1964, the total increase in female lung cancer deaths was only 2,400, averaging less than 500 per year for the period. The corresponding increase for male lung cancer deaths was 11,500. With so many millions of persons of both sexes smoking cigarettes regularly, parity in lung cancer mortality would have been reached a long time ago if tobacco was a causal factor. Observations in both the pre-cigarette and cigarette smoking eras have shown that the female is resistant biologically to lung cancer although vulnerable to other types of malignancy.

There is increasing evidence (232-234) that many of the cases diagnosed in females as primary lung cancer are, in actuality, metastatic cancers from the breast and genital organs.

The affinity of the lung for secondary growths from these organs is well established. In 1964, there were approximately 45,000 deaths reported from cancer of the breast, uterus, and ovary of which 26,000 deaths were attributed to cancer of the breast alone. With more than two-thirds of breast cancers and one-third of genital cancers metastasizing to the lung, there is created a vast potential for diagnostic error, particularly, in cases of solitary pulmonary metastases with occult tumors in the primary site. (262)

Greater histologic experience in the diagnosis of pulmonary tumors will manifest itself in subsequent years by more discriminatory diagnoses of lung cancer in females. There is already an inclination of this trend in the 1964 lung cancer mortality data. Of the 19,651 cases certified as primary lung cancer, there were 17,134 males and 2,517 females, giving a ratio of 6.8:1. In the 26,066 cases not certified as to primary or secondary origin there were 21,684 males and 4,382 females giving a ratio of 5:1. (See Table I, page 64 (a)).

Age Distribution

Lung cancer occurs predominantly in the older age groups with the majority of cases in the 5th, 6th, and 7th decades of life. The disease is unusual below the age of 40 and a rarity below the age of 30. Simons (234), in a collected series of more than 5,000 cases found that 80 per cent had occurred between 40 and 70 years of age. This distinctive age distribution was noted

TABLE I

LUNG CANCER MORTALITY

Classification of Cases According to 7th Revision of International Code

Lung Cancer	1959	1960	1961	1962	1963	1964
Classification No. 162.1 (Specified as primary)	17,042	18,342	19,462	18,749	18,868	19,651
Classification No. 163 (Unspecified as to whether primary or secondary)	17,139	18,978	19,467	22,510	24,569	26,066

It is evident from Table I that the major portion of the rise in lung cancer mortality between 1959 and 1964 was in classification No. 163 which showed an increase of 8,927 cases (52.0 per cent). The increase in classification No. 162.1 was only 2,609 cases (15.3 per cent). Between 1961 and 1964 the increase in classification No. 162.1 was negligible whereas, in classification No. 163, there were 6,599 additional cases. These figures are indicative of greater discrimination in the diagnosis of primary lung cancer by the certifying physicians. The increase in classification 163 connotes greater awareness of the possibilities of metastatic lung cancer simulating bronchogenic carcinoma. It has been stated by the advocates of the epidemic concept that the failure to specify primary lung cancer on death certificates is merely an oversight. According to this misguided interpretation the lung cancer mortality figures since 1961 imply a steady increase in laxity in the medical profession inasmuch as the apparent oversight is getting progressively larger.

in the 19th century (77,31,105,157) in the absence of cigarette smoking and also in recent decades in the era of widespread cigarette consumption (122,173,235,236). The relationship between longevity of the population and the incidence of lung cancer is therefore very significant.

During the past 50 years there has been a spectacular increase in the life span for all subdivisions of the population (237). In the period 1900-1902, the life expectancy at birth for white males was 48.23 years; in 1959-1961, the life expectancy had increased to 67.55 years. The life expectancy for white females was 51.08 years in the period 1900-1902 and 74.19 years in the period 1959-1961. This increase in the life span was even more striking in the non-white population. Non-white males had a life expectancy of 32.54 years in 1900-1902 and this increased to 61.48 years for the period 1959-1961. During the same interval the life expectancy for non-white females rose from 35.04 years in 1900-1902 to 66.47 years in 1959-1961.

Comparative studies on mortality rates present problems because of the limited number of states in the registration area in the early part of the century. Some degree of accuracy may be ascertained by comparing the life span per 100,000 persons over a period of several decades. In 1900-1902, of every group of 100,000 white males born alive, only 46,452 reached 60 years of age. Sixty years later, the statistical picture was entirely different. In 1959-1961, there were 75,485 white males

out of every 100,000 who reached 60 years. The corresponding increase among white females was from 50,752 in 1900-1902 to 86,339 in 1959-1961. Improvements in medical care, greater availability of diagnostic and therapeutic facilities, and higher economic standards of living were reflected in increased longevity of the non-white population. Whereas in the period 1900-1902, there were only 24,194 non-white males who attained 60 years of age, in 1959-1961, the number had increased to 61,669. The corresponding increase among non-white females was from 27,524 to 69,941.

The population of the United States is now considerably older than that in existence in the first decade of the 20th century. Within 50 years, the average duration of life increased 19.32 years for white males, 23.11 years for white females, 28.94 years for non-white males, and 31.43 years for non-white females. Current statistical reports (238) show no indication of abatement of the trend toward longer life expectancy. For 1965, the estimated expectation of life at birth was 70.2 years for the total population. It is very evident that, regardless of any hypothetical etiologic considerations, the total number of potential subjects for lung cancer has increased by many millions during the past half century. The inherent biologic characteristic of the disease to develop in older age groups will therefore result in the occurrence of more cases in future years as proportionately more of the population reaches the later decades of life.

Age at Onset

The predilection of lung cancer for the older age groups has a definite relevancy to etiologic considerations. If cigarette smoking produces a cumulative carcinogenic effect over a period of years then the segment of the population that began cigarette smoking in the early teen ages should develop lung cancer at a far younger age than those persons who began smoking at 30 to 40 years of age. There is also to be considered the effect of heavier smoking habits. Cigarette consumption per capita was only 50 per year at the turn of the century and by 1960 it had increased to 4,000 per year. It would seem reasonable to expect that if cigarettes were a carcinogenic hazard to health, the increased consumption would have resulted in a lowering of the age of occurrence of lung cancer. The fact is that neither the age at onset of smoking nor the number of cigarettes consumed has had any appreciable effect on the age of distribution of lung cancer which has remained a constant biologic feature since the disease was described 150 years ago.

In 1962, Passey (239) reported an investigation of 415 males with lung cancer to determine the effect of smoking on onset of the disease. The results showed that lung cancer had been acquired at approximately the same age regardless of whether smoking had been started at 6 years or at 41 years of age. Equally significant was the finding that the number of cigarettes smoked daily did not affect the age at onset; in both the light smokers

and the heavy smokers the disease had developed during the same decades of life. In 1965, Pike and Doll (240) studied a group of British doctors with lung cancer equating the consumption of cigarettes with the average age at death. Among the doctors who began to smoke at 17 years of age, the average age at death was 71.8 years for the light smokers and 69.3 years for the heavy smokers. The duration of smoking was also equated with the average age at death. Among those who smoked 15-24 cigarettes daily since the age of 17 years, the average age at death was 70.5 years; among those who consumed the same amount but began to smoke at 32 years of age, the average age at death was 75.0 years; and among those who started to smoke at 42 years, the average age at death was 78.0 years. The differences in age at death between the groups may be statistically significant but have little clinical importance because of the variety of conditions that contribute to mortality in the 8th decade of life.

Experimental Confirmation

A statistical association between two variables is not proof of a causal relationship. It is regrettable that this obvious axiom should have eluded the Surgeon General's Advisory Committee so completely. There is a very high degree of correlation between automobile accidents and being fully clothed but the latter is in no way responsible for the former. A statistical association, per se, has little meaning unless there is also established a biologic or physical relationship between the two

phenomena. In the case of the smoking-lung cancer association, no definite biological confirmation has been obtained despite the numerous attempts to produce bronchogenic carcinoma in the experimental animal.

Most of the experiments have involved mice because of the tendency of certain strains to develop lung tumors spontaneously. Uniformly negative results were obtained by Campbell (241) in 1936, Lorenz (242) in 1943, Essenberg (243) in 1952, and Leuchtenberger (244) in 1960. In not a single instance had the disease been produced experimentally by exposure to tobacco smoke. Another form of experimentation involved the direct application of tobacco extracts or smoke condensates. This, too, could not produce bronchogenic carcinoma (245,246) except for one glaring exception (247) in which the disease was produced in 1 out of 130 experimental animals. In the customary appraisal of scientific experiments these findings would be given important consideration in evaluating causal relationships but the Advisory Committee dismissed them as incidental and subtly invalidated the negative results with irrelevant sophistries.

In one section of the Report dealing with the chemical composition of cigarette smoke it is stated that polycyclic aromatic hydrocarbons are carcinogenic in rodents and that therefore one can reasonably presume that the same substances may also be carcinogenic in one or more tissues in man. The Report then cited evidence that skin cancer can be induced by certain industrial hydrocarbons and concluded that inasmuch as some of

these substances were present in tobacco smoke, the latter should also be assumed to be carcinogenic. This specious syllogistic reasoning implicating tobacco as a cancer producing substance in man seems a very weak argument when confronted by the many million-years of exposure of the fingers of smokers to tobacco smoke without producing cancer of the skin. The low prevalence rate of lung cancer in smokers also fails to substantiate the thesis that the hydrocarbons in cigarette smoke are carcinogenic in man. In a matched study of 36,975 smokers and an equal number of non-smokers, Hammond (248) found 110 lung cancers in the smokers and 12 in non-smokers. There were 9 times as many cancers in the smokers but the prevalence rate was only 0.3 per cent, or, 1 lung cancer in every 336 smokers. It is difficult to reconcile the alleged carcinogenicity of cigarettes with the failure to produce the disease in 36,863 (99.7 per cent) smokers.

Pathologic Studies

In an attempt to provide a biologic parameter for the statistical association between smoking and lung cancer, the Advisory Committee referred to certain studies (249-251) showing alterations in the epithelial lining of the respiratory tract of smokers. The changes had been found in smokers and also in lung cancer patients and from this the Committee deduced that the changes probably represented precancerous conditions thereby providing the missing link between smoking and lung cancer. Unfortunately, the Committee was unaware that the pathologic findings

in smokers were located in those parts of the bronchial tubes in which lung cancer seldom develops. The most advanced precancerous changes were found equally distributed among the large and small bronchial tubes whereas it is now well established (252-254) that lung cancer originates predominantly in the smaller bronchi or more peripherally.

The tendency for the alleged precancerous conditions to occur in parts of the lung seldom involved by lung cancer was also observed in a study (255) similar in scope to those cited in the Report. It was found, paradoxically, that the most advanced changes occurred at the bifurcation of the largest bronchi where lung cancer rarely originates and that the pathologic changes were least evident in the smaller bronchi where the disease develops most frequently. A study (256) of the distribution of inhaled smoke also revealed an inverse relationship between the sites of smoke concentration and those of lung cancer origin with the greatest concentration of smoke found below the trachea. It appears from these studies that in those parts of the lung with the greatest concentration of smoke and the most precancerous changes there is found the smallest number of lung cancers.

It must be emphasized that the alleged precancerous changes observed in the bronchial epithelium of smokers are the same changes that have been observed in patients with inflammatory diseases of the lung for many decades prior to the era of

widespread cigarette smoking. As early as 1876 it was noted that one of the complications of pneumonia was an atypical growth of cells of the bronchial mucosal lining and similar changes were described in 1895 in tuberculosis (257,105). In 1920, a monograph on the pathology of influenza depicted these changes most vividly (258). The pathologic alterations identified by the Advisory Committee with cigarette smoking occur commonly in a variety of diseases including bronchiectasis, bronchopneumonia, and lung abscess. They represent the natural protective response of the bronchial epithelial cells against trauma and occur in smokers and non-smokers. Newly formed cells proliferate from the germinal layer of epithelium to form a new type of tissue resembling squamous epithelium. These changes are very common and, it they led to lung cancer, the incidence of the disease would be many times greater.

The Report also identifies certain types of lung cancer with smoking and other types with non-smoking according to the classification of Kreyberg, a Norwegian pathologist (259). This concept bolsters the smoking - lung cancer hypothesis but is incorrect in its premise. Recent studies (260) have shown that the histologic types of lung cancer are definitely related to the site of origin in the bronchial tract. The squamous and oat cell carcinomas arise predominantly from the segmental bronchi and the adenocarcinomas arise chiefly from the minute bronchi, or distally. All bronchial epithelium has a common embryologic

origin and the various histologic types and structural features of lung cancer are determined by the site of origin, degree of differentiation, and environmental surroundings. It was also found that lung cancer occurs predominantly in only a few segments of the lung and uncommonly in the other parts of the lung. It is difficult to reconcile this finding with the smoking hypothesis unless it is assumed that cigarette smoke has a preternatural affinity for these particular areas.

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